Evidence Report/Technology Assessment
Number 216

Antidepressant Treatment of Depression During Pregnancy and the Postpartum Period

Executive Summary

Background

Depression is a potentially life-threatening condition. The incidence of depression during pregnancy and the postpartum period is estimated to be anywhere from 5.5 to 33.1 percent, and the American Academy of Pediatrics estimates that more than 400,000 infants are born each year to mothers who are depressed.[1-3]

Depression during pregnancy is known to be associated with harmful prenatal health consequences, such as poor nutrition, poor prenatal medical care, risk of suicide, and harmful health behaviors (e.g., smoking and alcohol or other substance misuse). These circumstances compromise the health of both the woman and her fetus.[4,5] Although causation has not been proven, several obstetric complications have been reported with untreated prenatal depression, including preeclampsia, preterm delivery, low birth weight, miscarriage, small-for-gestational-age babies, low Apgar scores, and neonatal complications. These complications may be more common among women with lower socioeconomic status.[6-8] In addition to being debilitating for the mother, postpartum depression affects maternal-infant interactions and some measures of infant development. In extreme cases, postpartum depression may increase the risk of infant mortality through neglect, abuse, or homicide.[9] It also negatively affects interactions within other members of the family unit and is associated with intimate partner violence.[10]

Evidence-based Practice Program

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov/reports/final.cfm.

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Evidence-Based Practice

A 2013 Agency for Healthcare Research and Quality (AHRQ) report found that screening can significantly reduce postpartum depressive symptoms when systems are in place to ensure adequate followup of women with positive results.[11] Management of depression in pregnancy or the postpartum period varies case by case; providers and patients are often concerned about the safety of pharmacological treatment during pregnancy and the postpartum period.[12]

Clinicians can use interventions such as pharmacological treatments, nonpharmacological treatments, and watchful waiting for patients with depression, both during pregnancy and in the postpartum period; they may also elect not to provide any intervention at all. Pharmacological treatments approved by the U.S. Food and Drug Administration (FDA) for treating depression are listed in Table A. Antidepressant medications have been shown to be effective at reducing the symptoms of depression in nonpregnant adults.[13,14] In general, medications that are effective in treating conditions outside of pregnancy are often presumed to remain effective in pregnancy, but the developing fetus and changes in maternal physiology raise questions about safety and dosing of various agents. For safety of the fetus, the FDA Pregnancy Category of antidepressant medications taken during pregnancy is category C ("animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks"), with the exception of paroxetine, which is category D ("there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks"). However, evidence on how the risk of one antidepressant compares with that of another when taken during pregnancy is not well understood. Antidepressant medications are used to treat a variety of other indications, including anxiety disorders such as generalized anxiety disorder, panic attacks, obsessive compulsive disorder, depressed phase of bipolar disorder, and neuropathic pain.

A wide array of nonpharmacological interventions can be used to treat depression, including various psychotherapies, electroconvulsive therapy, repetitive transcranial magnetic stimulation, and acupuncture.[15-19] Some of these may be used during pregnancy, whereas others may be reserved for use in the postpartum period (e.g., electroconvulsive therapy). Decisionmaking surrounding treatment of depression in pregnancy is complex because the harms of treatments must be balanced against the potential harms to mother and fetus of untreated depression.

Objectives

The objective of this systematic review was to evaluate the benefits and harms of various pharmacological treatment options for depression during pregnancy and the postpartum period compared with each other, with nonpharmacological treatments, and with usual care or no treatment.

Key Question 1. What are the comparative benefits of pharmacological and nonpharmacological treatments for women with depression during pregnancy and in the postpartum period?

a. How do pharmacological treatments affect maternal and childa outcomes when compared with placebo or no active treatment or usual care?

b. How do pharmacological treatments affect maternal and child[a] outcomes when compared with each other (drug A vs. drug B)?

c. How do pharmacological treatments affect maternal and child outcomes when compared with active nonpharmacological treatments?

d. How does combination therapy affect maternal and child outcomes? The combinations include:

   i. Using a second drug to augment the effects of the primary drug and comparing this treatment with monotherapy with a single drug

   ii. Combining pharmacological treatments with nonpharmacological treatments and comparing them with nonpharmacological treatments alone

   iii. Comparing pharmacological treatments alone with pharmacological treatments used in combination with nonpharmacological treatments

Key Question 2. What are the comparative harms of pharmacological and nonpharmacological treatments for women with depression during pregnancy and in the postpartum period?

a. How do pharmacological treatments affect maternal and child[a] outcomes when compared with placebo or no active treatment or usual care?

[a]A child is defined as a fetus, infant, or child younger than age 18.

b. How do pharmacological treatments affect maternal and child outcomes when compared with each other (drug A vs. drug B)?

c. How do pharmacological treatments affect maternal and child outcomes when compared with active nonpharmacological treatments?

d. How does combination therapy affect maternal and child outcomes? The combinations include:

   i. Using a second drug to augment the effects of the primary drug and comparing this treatment with monotherapy with pharmacological treatment

   ii. Combining pharmacological treatments with nonpharmacological treatments and comparing them with nonpharmacological treatments alone

   iii. Comparing pharmacological treatments alone with pharmacological treatments used in combination with nonpharmacological treatments

e. In babies born to women who become pregnant while taking medications to treat depression, what is the comparative risk of teratogenicity?

Key Question 3. Is there evidence that the comparative effectiveness (benefits or harms) of pharmacological and nonpharmacological treatments for women with depression during pregnancy and in the postpartum period varies based on characteristics[b] such as:

a. Patient characteristics—race, age, socioeconomic status, family history of depressive or mood disorders, prior use of antidepressive drugs (for treatment or prevention), severity of symptoms, situation at home, unplanned pregnancy, and marital or partner status?

b. Patient comorbidities (e.g., anxiety diagnoses)?

c. Intervention characteristics—dosing regimens and duration of treatments?

d. Coadministration of other psychoactive drugs—specifically, antipsychotics, antianxiety agents (e.g., benzodiazepines), and drugs for insomnia?

e. Medical provider characteristics (primary care physician, obstetrician, pediatrician, psychiatrist, nurse, midwife, or community worker)?

f. Medical care environment (community, private, or public clinic or hospital)?

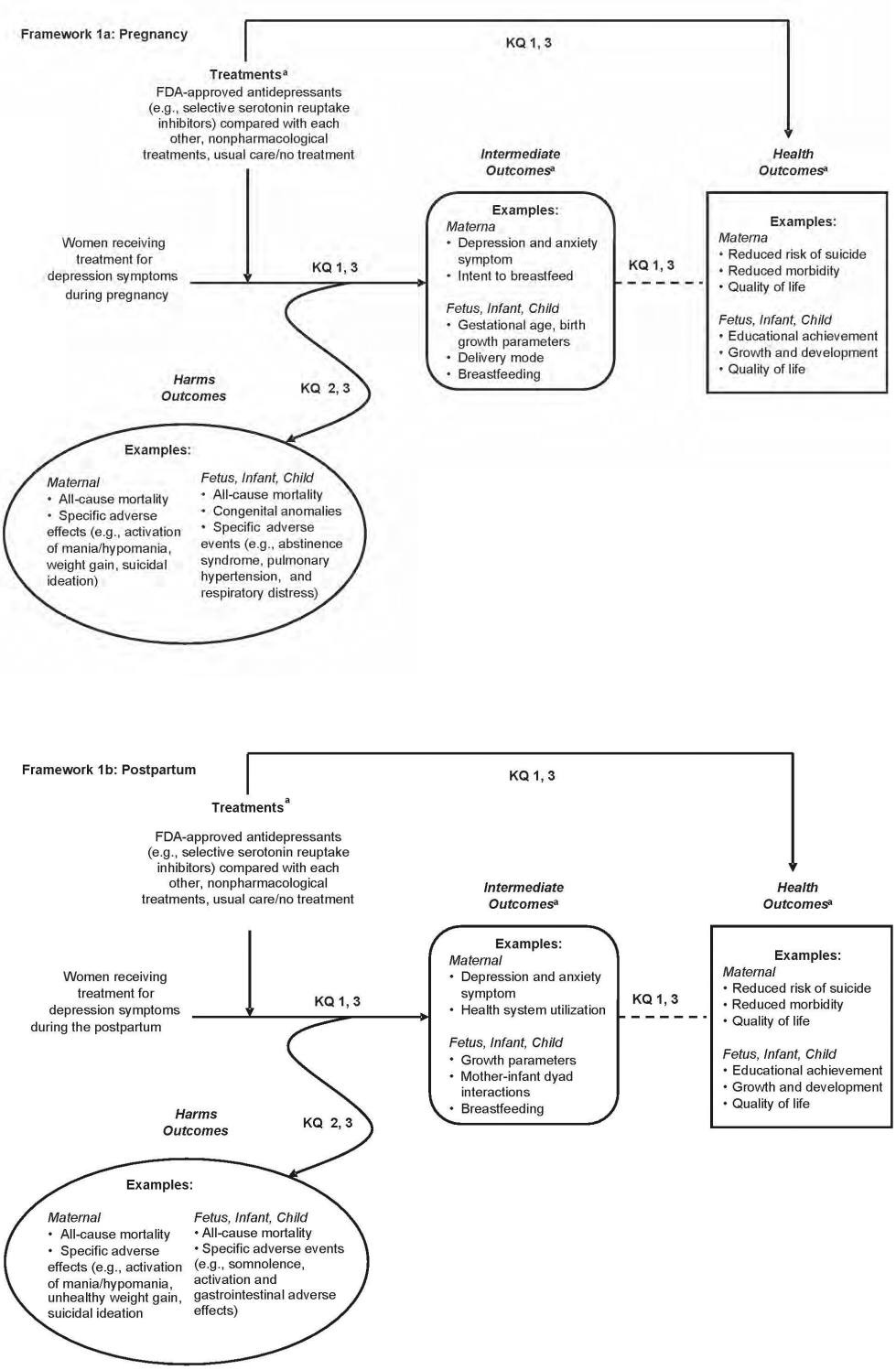
g. Characteristics of diagnosis—whether depression was detected during screening or not, time of diagnosis, method of diagnosis, and when treatment commenced relative to the onset of symptoms?

Analytic Frameworks

The analytic frameworks (Figure A) illustrate the population, interventions, outcomes, and adverse effects studied and their relationship to the Key Questions. Framework 1a relates to pregnant women with depression who receive treatment. Treatment leads to health outcomes, shown in the box on the far right of the figure and connected by the overarching line. This evidence is the topic of Key Question 1, as marked on the line. Treatment may lead to intermediate outcomes, such as changes in level of depression symptoms, or adverse events, both noted separately on the diagram. The evidence showing that better intermediate outcomes (e.g., symptoms) improve health outcomes (e.g., reduced risk of suicide) is represented by a dotted line between boxes; we did not review that literature in this report. Framework 1b relates to postpartum women with depression, and again the outcomes that may result from treatment are depicted in relationship to each other, the treatments, and Key Questions. The outcomes considered differed from those considered for pregnant women.

[b]Other factors will be considered as they are identified within the comparative studies.

Figure A. Analytic frameworks for treatment of depression in pregnant and postpartum women



[a] The interventions and outcomes are too numerous to illustrate in their entirety in this diagram. See the Methods section below (Inclusion and Exclusion Criteria) for complete details on interventions and outcomes.

FDA = U.S. Food and Drug Administration; KQ = Key Question.

Methods

The methods for this Comparative Effectiveness Review follow the methods suggested in the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (available at www.effectivehealthcare.ahrq.gov/methodsguide.cfm).[20] The methods reported here reflect the protocol elements established for Comparative Effectiveness Reviews and methods mapping to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist.[21] All methods and analyses were determined a priori. The research protocol was posted on the AHRQ Effective Health Care Program Web site (www.effectivehealthcare.ahrq.gov), and we registered the protocol in the systematic review registry, PROSPERO (www.crd.york.ac.uk/NIHR_PROSPERO/; record # CRD42013004493).

Literature Search Strategy

To identify studies relevant to each Key Question, the librarian searched the Cochrane Database of Systematic Reviews (CDSR) from 2005 to July 2013, the Cochrane Central Register of Controlled Trials (CCRCT) from 1980 to July 2013, the Cumulative Index to Nursing and Allied Health Literature (CINAHL®) from 1941 to July 2013, Ovid MEDLINE® and Ovid OLDMEDLINE® (1946 to July 2013), PsycINFO® (1806 to July 2013), and Scopus® (1974 to July 2013). ClinicalTrials.gov was searched for gray literature. The AHRQ Scientific Resource Center solicited Scientific Information Packets from industry stakeholders.

Inclusion and Exclusion Criteria

Populations

We defined the populations of interest as pregnant women and women during the first 12 months after delivery who received treatment for a depressive episode, including:

- Women with a diagnosis for major depressive disorder according to the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)[22]
- Women with subthreshold depressive symptoms

This report focuses chiefly on women diagnosed with depression during pregnancy or the postpartum period, rather than those with a continuing episode. The one exception is for Key Question 2e, regarding teratogenicity of antidepressant drugs taken during the conception period.

Based on input from experts, we also included studies with populations of pregnant women receiving antidepressant drugs for unknown or mixed reasons. We used these studies to provide evidence when no evidence was available on women with known depression or depressive symptoms (gaps in the evidence). To differentiate these populations, in this report we refer to studies of women with known depression as "treated" or "untreated" populations. We refer to studies of women with mixed or unknown diagnoses in terms of "maternal exposure" when receiving antidepressants (at typically unknown doses) and "maternal nonexposure" when not receiving antidepressants.

Interventions

Interventions include commonly used antidepressant drugs listed in Table A. We used the therapeutic classifications used in previous AHRQ comparative effectiveness reviews:[13,14] selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor (SNRI), selective serotonin norepinephrine reuptake inhibitor, and tricyclic antidepressant (TCA), except that we classified trazodone and nefazodone as norepinephrine reuptake inhibitors (NRI) for this report.

Table A. Pharmacological interventions: antidepressant agents

Drug Category	Generic Name	Trade Name[a]
Selective serotonin reuptake inhibitor	Citalopram	Celexa®, various generics
	Escitalopram	Lexapro®
	Fluoxetine	Prozac®, various generics Prozac Weekly® Sarafem®
	Fluvoxamine	Luvox®, various generics Luvox CR®
	Sertraline	Zoloft®, various generics
	Paroxetine	Paxil®, various generics Paxil CR®
	Vilazodone	Viibryd®
Serotonin norepinephrine reuptake inhibitor	Desvenlafaxine	Pristiq®
	Venlafaxine	Effexor XR®
	Mirtazapine	Remeron®, various generics Remeron SolTab®
Selective serotonin norepinephrine reuptake inhibitor	Duloxetine	Cymbalta®
Tricyclic antidepressant	Amitriptyline	Various generics
	Desipramine	Norpramin®, various generics
	Imipramine	Tofranil®, various generics
	Nortriptyline	Aventyl hydrochloride® Pamelor™ Various generics
Norepinephrine reuptake inhibitor	Nefazodone	Various generics (previously available as Serzone®)
	Trazodone	Desyrel®, various generics
Other	Bupropion	Wellbutrin® Wellbutrin SR® Wellbutrin XL® Forfivo XL® Aplenzin®

[a]CR, SR, XL, and XR abbreviations all refer to extended-release formulations.

Comparators

The comparators were:

- Placebo or no treatment.
- Usual care.
- The drugs in Table A compared with each other
- Any nonpharmacological treatment. We recognize the important differences between these treatments and consider them separately when compared with pharmacological treatments, rather than as a group.

Outcomes

Table B presents the included maternal, fetal, infant, and child benefits and harms outcomes.

Table B. Maternal and child benefits and harms outcomes included in the review

Benefit or Harm	Mother	Fetus, Infant, Child
Benefit Outcomes	• Danger to self—suicidal and nonsuicidal behaviors • Danger to infant—infanticidal behavior, abuse, or neglect • Depression symptomatology as scored using validated scales measuring depression: response, remission, speed and duration of response or remission, relapse, recurrence • Anxiety symptoms as scored as a subscale item using validated scales measuring depression or validated scales used to measure anxiety symptoms • Functional capacity – Quality of life using validated scales—e.g., Medical Outcomes Survey 36-item Short Form (SF-36) – Caring for self, infant, and family – Mother-father dyad interaction success, including reduced violence among intimate partners – Work productivity • Delivery and postpartum parameters – Breastfeeding – Shared decisionmaking around delivery choices (e.g., cesarean) and delivery mode – Mother-infant dyad interaction patterns – Pregnancy weight gain within or outside of 1990 Institute of Medicine Guidelines • Social services use; prevention of child protective service involvement • Maternal health system resource use, including emergency department use, hospitalizations, and office visits • Adherence or persistence with treatment regimen	• Parameters at birth and up to 12 months of age: preterm birth (e.g., < 32 weeks, < 37 weeks); appropriate growth (height, weight, and head circumference); gestational age (e.g., small for gestational age with race or ethnicity taken into consideration); birth hospitalization length of stay; infant attachment; developmental screening—Ages and Stages Questionnaire, Denver, Modified Checklist for Autism in Toddlers, Bayley Scales of Infant Development • Growth and development after 1 year of age – Developmental screening and diagnoses; growth parameters, such as height, weight, and body mass index percentile according to sex and age – Learning (e.g., linguistic, cognitive, and social-emotional skills) and educational achievement; kindergarten readiness; age at kindergarten entry; third grade testing outcomes; other standard testing outcomes (eighth grade, etc.) – Intelligence tests (any), individualized education plans, use of school services – School failure or dropout rate, high school graduation rate, missed school days • Stress-related chronic disease; mental and chronic illness • Infant health system visits (e.g., well-baby visits); health care use, including primary care, emergency department, hospitalization • Social services use—Women, Infants, and Children Program (WIC), community health nurse, social worker, State Department of Health and Human Services, free or reduced-price lunch, and Food Stamps • Community resource use • Social and emotional development; quality of life Contact with juvenile justice system

Table B. Maternal and child benefits and harms outcomes included in the review (continued)

Benefit or Harm	Mother	Fetus, Infant, Child
Harm Outcomes	• Death, including suicide, all-cause mortality, and cause-specific death (e.g., cardiac death) • Specific adverse effects or withdrawals due to specific adverse events related to treatment (e.g., hyponatremia, activation of mania or hypomania, seizures, suicidal ideation, hepatotoxicity, weight gain, metabolic syndrome, gastrointestinal symptoms, and loss of libid0) • Overall adverse-event reports, adverse events associated with discontinuation of treatment, and serious adverse events • Withdrawals from study and discontinuation of treatment due to adverse events	• All-cause mortality • Congenital anomalies (any) stratified into major and minor with further grouping by organ system or type of anomaly • Other specific adverse events, such as withdrawal symptoms (neonatal abstinence symptoms), pulmonary hypertension, respiratory distress, neonatal convulsions, and heart defects

Study Designs

For effectiveness, we used a "best evidence" approach. Top-tier evidence included randomized controlled trials (RCTs) and systematic reviews comparing pregnant women receiving pharmacological treatments for depression during pregnancy with control groups of pregnant women with depression who were treated with nonpharmacological treatments or untreated. If we found no or only very few RCTs, we included observational study evidence and studies that had control groups of nonexposed pregnant women.

For harms, in addition to RCTs and systematic reviews, we included observational studies comparing women receiving pharmacological treatments for depression during pregnancy with control groups of pregnant women with depression who were treated with nonpharmacological treatments or had no treatment. If insufficient evidence was found, studies that compared with control groups of nonexposed pregnant women were included.

Case reports, case series, and single-group studies were excluded.

Study Selection

Two reviewers independently assessed titles and abstracts of publications identified through literature searches using the criteria described above for inclusion and exclusion of studies. Two reviewers assessed potentially relevant full text. Disagreements were resolved by consensus or a third-party arbitrator.

Data Extraction

Key study characteristics were abstracted from included studies into evidence tables. One reviewer abstracted study data and a second reviewer did random checking. Intention-to-treat results were recorded if available.

Risk-of-Bias Assessment of Individual Studies

We assessed the risk of bias (internal validity) based on predefined criteria established by the Drug Effectiveness Review Project.[23] We rated the internal validity of observational studies based on the adequacy of the patient selection process, whether important differential loss to followup or overall high loss to followup occurred, the adequacy of exposure and event ascertainment, whether acceptable statistical techniques were used to minimize potential confounding factors, and whether the duration of followup was reasonable to capture investigated events.

All assessments resulted in a rating of high, medium, or low risk of bias, primarily at the study level. In some cases, the reviewers determined that validity varied by outcome and rated risk of bias for different outcomes separately. Studies that had serious flaws were rated high risk of bias, studies that met all criteria were low risk of bias, and the remainder were medium risk of bias. All studies were rated by one reviewer and checked by another reviewer. All disagreements were resolved through consensus.

Based on input from experts, we identified as key for all outcomes four potential confounding factors to be adjusted for in analyses of observational studies—age, race, parity, and other exposures (e.g., alcohol, smoking, and other potential teratogens). In some cases, additional confounders were considered based on their particular relevancy to

specific outcomes. Low or moderate risk-of-bias studies that adjusted for these confounders were considered the best evidence if no RCTs were available.

Data Synthesis

We preferred direct comparisons over indirect comparisons, so they are the focus of our synthesis. We considered three types of directness: populations, intervention comparisons, and outcomes. Direct evidence consists of studies that (1) included the population of interest—depressed pregnant or postpartum women—in both intervention and control groups; (2) made the comparisons of interest—pharmacological treatments compared with each other, nonpharmacological interventions, or no treatment; and (3) measured outcomes of interest directly and did not use proxy measures (e.g., laboratory values). In this report, direct evidence included studies (trials or observational studies) that compared pregnant or postpartum women with depression who received antidepressant treatment with pregnant or postpartum women with depression who were not treated.

Indirect evidence included studies (trials or observational studies) of pregnant or postpartum women treated with antidepressants without specifying that the women had depression. Similarly, studies that compared pregnant or postpartum women who took an antidepressant drug with pregnant or postpartum women who did not take such medications but also were not known to have a diagnosis of depression (a general population) were considered indirect evidence. Indirect comparisons can be difficult to interpret for several reasons; in the case of comparison with a general population, the issue is primarily heterogeneity of underlying risk of the populations.

The underlying risk of untreated depression during pregnancy or the postpartum period is an important factor in assessing the relative benefits and harms of potential treatments. We used data from indirect comparisons when no other directly applicable evidence existed, but readers should interpret findings with caution because comparisons with a generally healthy population without depression rather than with a depressed population may underestimate the benefits and overestimate the harms of treatment.

We generally did not use data from high risk-of-bias studies in our main analysis, except to undertake sensitivity analyses for meta-analyses or when high risk-of-bias studies constituted the only evidence for an important outcome. To determine the appropriateness of meta-analysis, we considered the risk of bias of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. We generally used random-effects models to estimate pooled effects; when only two studies were being pooled, we applied a fixed-effect model.[24,25] We calculated the Q statistic and the I2 statistic to assess heterogeneity in effects between studies.[26,27] When we found statistical heterogeneity, we explored reasons for this by using subgroup analysis. When we could not perform meta-analysis, we summarized the data qualitatively, grouping studies by similarity of population, intervention characteristics, or both.

Strength of the Body of Evidence

We used the methods outlined in the original Chapter 10 of the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews"[20,28] to grade strength of evidence. Domains considered in grading the strength of evidence were risk of bias, consistency, directness, and precision. Based on this assessment, reviewers assigned the body of evidence a strength-of-evidence grade of high, moderate, or low. A rating of *high* means that we have high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effect, while a rating of *low* means that we have low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of the effect and to change the estimate.[20,28] In cases in which evidence did not exist, was sparse, or contained irreconcilable inconsistency, we assigned a grade of insufficient evidence. A rating of *insufficient* means that the evidence either is unavailable or does not permit estimation of an effect.

We consulted our technical experts to help us set priorities for the outcomes for grading. Specific outcomes selected for rating included the following for any comparison with at least moderate risk-of-bias evidence. For maternal outcomes, we graded danger to self or infant, depression symptomatology (response and remission), breastfeeding intention and duration, number with adverse events, discontinuation due to adverse events, and weight gain. For infant outcomes, we graded preterm birth, small for gestational age, neonatal mortality, congenital malformations, persistent pulmonary hypertension, infant and child neurodevelopment, intellectual function, educational outcome and school performance, mental health, and health care or social service use.

Applicability

We assessed applicability by examining the characteristics of the enrolled populations compared with those of target populations, characteristics of the interventions, and characteristics of the comparators. Technical experts identified items of particular interest that may affect applicability, which are reflected in the subgroups specified in Key Question 3.

Results

Results of Literature Searches

Based on electronic searches (3,405 citations), manual searches (53 citations), and scientific information packets (Forest Pharmaceuticals, Inc.; Jazz Pharmaceuticals; and Sanofi Aventis, U.S.), we identified a total of 3,458 potentially relevant citations. From these, we included 130 eligible unique studies in this report. The majority of the evidence was from observational studies (124 unique studies); we included only 6 RCTs.

Six RCTs and 15 observational studies provided direct evidence comparing treatments in groups of pregnant or postpartum women with depression. This is the primary evidence for this report. We included indirect evidence from 109 observational studies that included pregnant or postpartum women receiving an antidepressant drug for any reason and making comparisons with women who were not receiving an antidepressant drug during pregnancy or the postpartum period. Studies generally did not note the depression status of women in the intervention or control groups, although a few included depression as a confounder that investigators controlled for in analyses. This evidence is indirect for this report. We reported findings from these studies only for important outcomes for which evidence in pregnant women with depression did not exist or was sparse, particularly for serious harms for which even such indirect evidence may be useful in guiding clinical decisions. No studies compared an antidepressant drug with a nonpharmacological treatment; only a few had an intervention that involved use of a nonpharmacological treatment as an add-on to drug therapy.

Key Question 1

The overarching finding for Key Question 1 was that little evidence exists on the maternal benefits of antidepressant therapy specifically during pregnancy or the postpartum period. Studies were generally not designed to measure benefits (e.g., effect on depressive symptoms) when women were treated during pregnancy, and evidence did not allow comparisons among either the specific classes or individual drugs. Evidence on key outcomes and comparisons is lacking. Similarly, we have no information on the most effective dose of antidepressant drugs in pregnant women based on severity of symptoms or on either pharmacokinetic or pharmacodynamic alterations during pregnancy.

Maternal Benefits

Comparative evidence on depressive symptom response, anxiety, functional capacity, healthy maternal weight gain, and breastfeeding outcomes is insufficient to draw conclusions about the effects of antidepressant drugs in women with depression during pregnancy. Based on direct evidence from two very small observational studies, we found inconsistent results on the benefit of SSRI treatment on depressive symptoms during pregnancy and no evidence for other drug classes. A small observational study reported that depressed women treated with SSRIs continuously during pregnancy had higher scores on the SF-12 Mental Component Scale than did untreated women with depression throughout pregnancy (scores of 45 and 35, respectively, on a scale of 0 to 100), but the timing of measurement was not clear. We found no direct evidence of the effects of antidepressant drugs on other important depression outcomes, such as anxiety symptoms in women with depression during pregnancy. No direct evidence was available regarding pregnancy weight gain, intention to breastfeed, uptake of breastfeeding, or duration of breastfeeding.

Studies of pregnant women with unknown depression status provided indirect evidence on weight gain and breastfeeding outcomes. Such evidence was insufficient to draw conclusions about these outcomes in pregnant women with depression, but it may provide insight into directions for future research. Among pregnant women with unknown depression status, weight gain was slightly above recommended limits for women taking SSRIs but within recommended limits for women who did not receive SSRIs. Indirect evidence also suggested that, in pregnant women with unknown depression status, SSRI treatment during pregnancy was associated with fewer women intending to or initiating breastfeeding than among women not receiving such treatment during pregnancy; this probably reflects concerns or uncertainty about potential harms to the breastfed child. No evidence was available for comparative benefits of other pharmacological treatments in pregnant women with depression.

Evidence on maternal benefits from pharmacological treatments for depression during the postpartum period was insufficient. Direct evidence was limited to one small placebo-controlled trial that we rated as high risk of bias; indirect evidence came from a small observational study in pregnant women with unknown depression status rated medium risk of bias.

Evidence on the combination of antidepressant therapy with nonpharmacological interventions was insufficient to draw conclusions because of inconsistency and imprecision; it generally suffered from lack of adequate sample sizes.

Child Benefits

The potential benefits of treatment of depressed women during pregnancy to their children include parameters at birth (e.g., birth weight), child development, diagnosis of chronic diseases, and health care use. Direct evidence was available only for preterm birth and some developmental outcomes. Low-strength evidence from two small observational studies (N = 266 total) suggested that SSRIs have no statistically significant effect on rates of preterm birth (defined as <37 weeks gestation).[29,30] Pooled analysis yielded an odds ratio (OR) of 1.87 (95% confidence interval [CI], 0.89 to 3.89). Indirect evidence suggested increased risk of preterm birth for women treated with SSRIs, TCAs, SNRIs, or NRIs during pregnancy compared with the risk for women not treated with antidepressants during pregnancy and with unknown depression status. For SSRIs, this finding was consistent across studies; however, the magnitude of risk associated with specific timing of maternal exposure during pregnancy was unclear. Risk may be higher with citalopram or escitalopram than with fluoxetine, paroxetine, and sertraline; however, direct comparisons of the drugs in women with depression are needed to confirm these findings. Evidence on fetal growth was limited to indirect evidence; we found no apparent increased risk associated with exposure to SSRIs or TCAs.

Direct evidence on infant and child development was limited to two very small studies. This evidence was insufficient to draw conclusions about the risk of delayed development in children of mothers taking SSRIs for depression during pregnancy compared with the risk in children of mothers whose depression was not treated with antidepressants. Indirect evidence did not indicate increased risk of motor, language, or cognitive development that is outside of the normal range for age.

Comparative evidence on the risk of diagnosis of attention-deficit hyperactivity disorder (ADHD) in children of mothers treated for depression during pregnancy was insufficient; we had no direct evidence on this concern. Indirect evidence suggested that, compared with children not exposed during pregnancy, diagnosis by the age of 5 years among exposed children was associated with bupropion use (OR, 3.63; $p<0.02$), particularly for exposure in the second trimester. In contrast, a diagnosis of ADHD was not associated with use of SSRIs or other antidepressants during pregnancy. Filling a prescription for an SSRI after pregnancy (timing not defined) was statistically significantly associated with increased risk of ADHD diagnosis in the child by age 5 (OR, 2.04; $p<0.001$). These analyses controlled for parental mental health diagnoses; a diagnosis of depression in the mother during pregnancy was statistically significantly associated with the diagnosis of ADHD in the child (OR, 2.58; $p<0.001$).

Whether autism spectrum disorder (ASD) in the child is associated with depression during pregnancy, antidepressant treatment, or an interaction of the two was not clear. We found no direct evidence on the risk of different treatments for depression during pregnancy on development of ASD in the child. We found indirect evidence, based on two large population-based case-control studies with low and medium risk of bias, that suggested that maternal use of SSRIs is statistically significantly associated with diagnosis of ASD in the child after controlling for maternal depression diagnosis during pregnancy (pooled OR, 1.82; 95% CI, 1.14 to 2.91).[31,32] Both studies also examined antidepressant drugs other than SSRIs: one found an increased risk with TCAs and the other found no increased risk with TCAs combined with SNRIs or NRIs. Although these results controlled for depression, the comparison groups were children of women who did not receive an antidepressant during pregnancy rather than women with untreated known depression; moreover, neither study reported the proportion of women with a diagnosis of depression for either group.

In one of these studies, results of subgroup analyses suggested that depression itself may contribute to ASD diagnosis. Compared with the risk for ASD in children of pregnant women without depression or antidepressant use, the risk for ASD in the children of pregnant women with depression and antidepressant use was statistically significantly elevated (OR, 3.34; 95% CI, 1.50 to 7.47). In contrast, the risk in pregnant women taking an antidepressant for another indication was lower than the risk in children of pregnant women without depression or antidepressant use and not statistically significant (OR, 1.61; 95% CI, 0.85 to 3.06).

We found no evidence comparing drug therapy with nondrug therapy. Evidence for other outcomes or comparisons for exposure either during pregnancy or in the postpartum period was not found or was insufficient.

Key Question 2

Maternal Harms

We found no direct evidence on maternal harms of pharmacological treatments for depression during pregnancy. The main reasons are that, for this population, we had only observational evidence and the studies did not report harms outcomes of interest for this report, such as rates of specific adverse effects (e.g., suicidal ideation, hepatotoxicity, and loss of libido). The risk of mortality may have been reported sporadically, but most of these retrospective observational studies would have excluded women who died during pregnancy, and the remaining studies did not have explicit methodology to ascertain death and other serious harms.

Child Harms

Evidence on harms to the child of a mother treated for depression during pregnancy was limited by the comparison groups that most studies selected—namely, pregnant women who did not take an antidepressant and with unknown depression status. As with comparative benefits to the child, the direct evidence was very limited and was mostly insufficient for drawing conclusions. Indirect evidence may be valuable for harms such as mortality and congenital anomalies, because signals for increased risk of harm may be used to direct future studies. The findings for maternal treatment with antidepressants during pregnancy reflected evidence of greater risk for some serious infant harms associated primarily with exposure to SSRIs, but the contributory role of depression in these outcomes is mostly unstudied.

We had no direct evidence for the risk of infant mortality with maternal use of antidepressant drugs to treat depression during pregnancy. Indirect evidence, based on large population-based cohort studies, was inconsistent; study findings indicated an increased risk of infant death over the first year of life with exposure to SSRIs (OR, 1.81; 95% CI, 1.26 to 2.60), but not when we evaluated early and late death separately. A single cohort study reported no increased risk of neonatal mortality with SNRI or NRI use during pregnancy.

Direct evidence on the association of major congenital malformations with use of SSRIs for depression during pregnancy was insufficient, based on two small studies (N = 282 total) that reported only one or zero events. No comparative evidence on the risk of cardiac malformations in women treated for depression during pregnancy was found. A substantial amount of indirect evidence about the incidence of major congenital malformations was available from 15 cohort studies; they reported on incidence associated with the use of either any SSRI or specific SSRIs among depressed women during pregnancy compared with no use of SSRIs among women who were not known to be depressed. Although exposure to SSRIs as a group did not result in increased risk of major malformations in infants, evidence indicated small but statistically significant risk with exposure to fluoxetine (OR, 1.14; 95% CI, 1.01 to 1.30) or paroxetine (OR, 1.17; 95% CI, 1.02 to 1.35), but not the other SSRIs individually. Timing of exposure was primarily in the first trimester, although our sensitivity analyses removing studies that may have included exposures at other timepoints did not alter these results. Results were similar for cardiac malformations, except that limiting our analyses to the highest quality studies of fluoxetine yielded a nonsignificant increase in risk. The increased risk with paroxetine was 1.49 (95% CI, 1.20 to 1.85). TCAs were also significantly associated with increased risk for major malformations (OR, 1.31; 95% CI, 1.04 to 1.65) and cardiac malformations (OR, 1.58; 95% CI, 1.10 to 2.29). Evidence for other antidepressants was not available.

We found no direct evidence on the risk of neonatal withdrawal symptoms or pulmonary hypertension with maternal use of antidepressant drugs to treat depression during pregnancy. Indirect evidence suggested greater risk of neonatal withdrawal symptoms with fluoxetine use for any reason (indications not specified or mixed) during the first trimester compared with women who did not use an antidepressant during pregnancy but whose depression status was unknown (relative risk, 8.7; 95% CI, 2.9 to 26.6). Risk was also found to be increased with SSRIs or venlafaxine in late pregnancy, but no difference in risk was found between SSRIs and SNRIs (as a group) in neonatal withdrawal symptoms. Indirect evidence suggested that persistent pulmonary hypertension in the child was statistically significantly associated with maternal SSRI use during late pregnancy (OR, 2.72; 95% CI, 1.63 to 4.54).

Based on three studies, there was low-strength evidence that, compared with untreated maternal depression during pregnancy, SSRI treatment was associated with a statistically significant increase in risk of respiratory distress in infants (pooled unadjusted OR, 1.91; 95% CI, 1.63 to 2.24; I2 = 0%). Direct evidence was not available to assess the risk with TCAs, SNRIs, or NRIs; however, indirect evidence suggested an increase in risk with TCAs used late in pregnancy (adjusted OR, 2.11; 95% CI, 1.57 to 2.83).

Low-strength direct evidence suggested no statistically significant associations between maternal use of SSRIs during pregnancy and neonatal convulsions compared with infants of untreated depressed pregnant women. Indirect evidence was in conflict with this finding, indicating an

increased risk of convulsions for children whose mother used SSRIs for any indication during pregnancy compared with the risk for children of women who did not take an SSRI during pregnancy and were not known to be depressed.

Only a few well-designed studies examined the risk for teratogenicity with exposure to antidepressants specifically during the conception period; the evidence was insufficient. Numerous other studies examined congenital malformations with exposure in early pregnancy but did not report on exposure during the conception period (i.e., pre-existing treatment). These studies contributed to the evidence on potential harms with treatment during pregnancy.

Key Question 3

In Key Question 3, we attempted to examine a wide range of subgroups defined by patient and intervention characteristics. Given the difficulty we had in identifying evidence for the first two Key Questions with appropriate control and intervention groups, it is not surprising that we found very little direct evidence to address these questions. Based on the direct evidence, with comparisons between treated and untreated pregnant women with depression and data stratified into continuous use and use during only one trimester, the duration of treatment did not appear to influence the risk of preterm birth. We found that, in the postpartum period, multiple sessions of cognitive behavioral therapy were not superior to a single session when both were combined with fluoxetine. Depressive symptom response to dynamic psychotherapy, with or without sertraline, did not vary based on depression severity level. For all other subgroups (including those based on coadministration of other drugs, medical provider characteristics, medical care environments, and characteristics of diagnosis), the evidence was limited. Studies that used a definite diagnosis of depression in all comparison groups and that had medium or low risk of bias provided only insufficient evidence to draw conclusions about variation in treatment effects.

Discussion

Table C highlights the findings based on studies that were designed to compare directly the benefits or the harms of pharmacological treatments for depression in pregnant or postpartum women. As noted, we regarded the results of these investigations as direct evidence. We believe that this is the best evidence for the Key Questions posed for this review.

Table C. Key findings of direct-comparison evidence for antidepressant treatment of depression during pregnancy or postpartum

Time of Treatment, Intervention, and Potential Benefits and Harms	Comparison	Outcome	Strength of Evidence; Conclusions
Pregnancy			
Potential Benefits:			
SSRIs + psychotherapy	Psychotherapy alone	Depressive symptoms	Insufficient; no conclusions drawn
SSRIs: fluoxetine	No treatment	Depressive symptoms	Insufficient; no conclusions drawn
SSRIs	No treatment	Functional capacity	Insufficient; no conclusions drawn
SSRIs + psychotherapy	Psychotherapy alone	Breastfeeding	Insufficient; no conclusions drawn
SSRIs	No treatment	Preterm birth	Low; risk not increased
SSRIs + psychotherapy	Psychotherapy alone	Infant and child development: Bayley Scales	Insufficient; no conclusions drawn
SSRIs	No treatment	Infant and child development: Brazelton Neonatal Behavioral Assessment Scale	Insufficient; no conclusions drawn
Potential Harms:			
SSRIs	No treatment	Major malformations	Insufficient; no conclusions drawn
SSRIs + psychotherapy	Psychotherapy alone	Major malformations	Insufficient; no conclusions drawn
SSRIs	No treatment	Neonatal convulsions	Low; risk not increased
SSRIs	No treatment	Neonatal respiratory distress	Low; risk higher with SSRIs
SSRIs	TCA: nortriptyline	Neonatal respiratory distress	Insufficient; no conclusions drawn
Postpartum			
Potential Benefits:			
Sertraline + brief dynamic psychotherapy	Brief dynamic psychotherapy	Depressive symptoms	Low; no difference in response or remission
Sertraline	Sertraline + interpersonal psychotherapy	Depressive symptoms	Insufficient; no conclusions drawn
Paroxetine	Paroxetine + cognitive behavioral therapy	Depressive symptoms.	Low; no difference in response or remission
Potential Harms:			
Sertraline + brief dynamic psychotherapy	Brief psychodynamic therapy	Adverse events	Insufficient; no conclusions drawn
Sertraline	Sertraline + interpersonal psychotherapy	Adverse events	Insufficient; no conclusions drawn

Table C. Key findings of direct-comparison evidence for antidepressant treatment of depression during pregnancy or postpartum (continued)

Time of Treatment, Intervention, and Potential Benefits and Harms	Comparison	Outcome	Strength of Evidence; Conclusions
Sertraline	Sertraline + interpersonal psychotherapy	Adverse events	Insufficient; no conclusions drawn
Fluoxetine + cognitive behavioral therapy	Cognitive behavioral therapy	Adverse events	Insufficient;

SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant

While the focus of this report is women with a new episode (not necessarily the first) of depression during pregnancy or postpartum, rather than a continuing episode, most studies simply identified women based on treatment status during pregnancy or postpartum (i.e., treated with antidepressants or not).

As reported in Table C, evidence for virtually all outcomes was insufficient. Only the outcomes of neonatal convulsions and respiratory distress in infants of women who took SSRIs as a class during pregnancy compared with those outcomes in infants of women with depression who did not take an antidepressant had low strength of evidence. The risk of convulsions was not higher with SSRIs; in contrast, the risk of respiratory distress was higher. For women with postpartum depression, only the evidence for depression symptom improvement with the comparison of adding brief dynamic psychotherapy or cognitive behavioral therapy to sertraline and paroxetine, respectively, was low strength, while the evidence for other outcomes was insuffucient. Adding these nonpharmacological treatments did not improve the response or remission of depression symptoms. The primary reason for the other direct evidence leading to a strength of evidence grade of insufficient—and thus our inability to draw any meaningful conclusions from this evidence—was that these were small studies. They may not have had adequate statistical power to identify differences when they existed and were not as methodologically strong as is necessary to draw firm conclusions.

Not shown are outcomes for which we had only indirect evidence. These included studies that compared outcomes for women who took an antidepressant during pregnancy for any reason with those for women who did not take an antidepressant during pregnancy; the proportions of women with depression in either group were rarely reported and never analyzed. The applicability of indirect evidence of findings from studies of pregnant women with unknown depression status is unclear.

Findings in Relationship to What Is Already Known

Putting these findings into the context of prior comparative effectiveness evidence reviews was difficult; we did not identify any other studies with as broad a scope as ours or other reviews that applied comparable methodologies. For example, a review by Bromley et al.[33] assessed fetal and child outcomes and SSRIs only, but those authors did not limit their comparison group to women with depression, so our results are quite different from theirs. Additionally, we formally assessed the risk of bias in individual studies and graded the strength of evidence for the body of evidence for each key outcome, which other reviews did not.[33-45]

Applicability

The evidence on the benefits and harms of pharmacological treatment during pregnancy was limited to observational studies that generally met criteria for effectiveness studies.[46] The evidence on benefits and harms of pharmacological treatment for postpartum depression came almost entirely from RCTs that met criteria for efficacy studies. These studies were limited by several factors: exclusion of patients with common comorbidities, such as drug and alcohol misuse or abuse, other Axis I disorders, and suicidal ideation; lack of health outcomes and comprehensive assessment of adverse events; short study durations; and small sample sizes.

Only a small group of studies included pregnant women known to be depressed and compared treated and untreated groups, providing direct evidence. In these studies, however, we did not have further information on the diagnosis timing, prior history, or severity of symptoms. As maternal depression is widely recognized as a risk factor for poorer pregnancy outcomes, the findings from all the studies that do not account for maternal depression likely have very low applicability to our target population of pregnant women with depression.

With respect to other variables, the mean maternal age ranged from 26 years to 34 years. Few studies reported race or socioeconomic status. In the studies that reported race, the populations were predominantly white. When reported, a medium socioeconomic status level was most common. The data sources for these studies typically did not include access to information such as depressive symptom severity, coexisting anxiety diagnoses, and other mental health or medical conditions; family history of depressive or other mood disorders; prior use of antidepressant drugs; situation at home; unplanned pregnancy; and marital or partner status. Therefore, we know very little about these important patient characteristics.

Very little evidence was available to assess the benefits and harms of nonpharmacological treatment modalities, and what we found was limited to treatment during the postpartum period. The clinical relevance of the nonpharmacological treatment modalities was difficult to assess because of a general lack of detail about the characteristics of these interventions. Likewise, the clinical relevance of the pharmacological treatment regimens was difficult to assess because of a general lack of information about dose, duration, and cointerventions.

Only approximately 30 percent of included studies were conducted in the United States. Findings from many of the studies done in the United States and Canada may not be reflective of the general population in North America because of their reliance on highly selected samples who voluntarily called teratogen information services, had specific health plan membership, or attended specific community prenatal clinics.

Overall, the applicability of this evidence to programs such as the Children's Health Insurance Program (CHIP) is somewhat limited because of the issues noted above. The large number of studies conducted in health care settings outside the United States and in samples of women with medium socioeconomic status likely limits how well this evidence applies to children served by the CHIP program.

Implications for Clinical and Policy Decisionmaking

Depression during pregnancy and postpartum can have adverse consequences for both mother and child. Knowing the best course of action when a woman is diagnosed with depression during these times is extremely important. For multiple reasons, the evidence base at present is extremely limited in the specific guidance it can provide.

Our overall findings were based on insufficient or low-strength evidence. This means that future studies are very likely to alter the findings in a meaningful way. The implications for decisionmaking for women with depression during pregnancy are unclear. Without better evidence specific to this population, the balance of benefits and harms is uncertain.

Although we believe that treating depressed women with antidepressants is likely to improve some symptoms based on evidence derived from studies of nonpregnant patients, individual drugs may have varying effects in pregnant women because of differences in pharmacokinetic parameters between these two types of patient populations. Current evidence is insufficient to address comparative efficacy in pregnant women. The evidence on functional outcomes for the mother is also insufficient, although it leans toward better outcomes in women treated with an SSRI than in untreated pregnant women. Evidence for other health outcomes in pregnant women is missing.

Women taking antidepressants during pregnancy or in the postpartum period may be less likely to breastfeed or may breastfeed for shorter durations than women who are not taking an antidepressant. Clinicians know that, for women treated with antidepressants, decisions about breastfeeding can be problematic; thus, early discussion and support for maternal intention to breastfeed is warranted. Women who receive prenatal education and professional encouragement or who report that their health care provider encouraged them to breastfeed are more likely to initiate and sustain breastfeeding.[47-49] Antidepressants are widely used in postpartum women. For most antidepressants, no or only negligible amounts are passed from mother to baby through breast milk (fluoxetine and citalopram may be exceptions, but the amount varies with dose and frequency of dosing); no evidence exists of adverse events in babies.[50-52]

Evidence on the comparative benefits of treating depression during pregnancy (compared with not treating) is expected to include benefits in developmental achievement in the child. Our review indicates that use of SSRIs did not result in differences on most measures. Although the direct evidence did not indicate higher rates of preterm birth with use of SSRIs during pregnancy (unadjusted OR, 1.87; 95% CI, 0.63 to 4.42), it was insufficient to guide clinical decisions.

It has been suggested that numerous potentially serious harms may be associated with use of antidepressants during pregnancy. In the comparison of treated and untreated depressed women, however, we found only the risk for neonatal respiratory distress to be associated with SSRIs (as a drug class). The fact that different conclusions may be drawn for some other outcomes based on a large body of evidence that we consider indirect for our questions highlights the importance of making clinically relevant comparisons.

An example is the risk of ASD in children of women treated for depression during pregnancy. The increasing prevalence of ASD diagnosis, likely in part attributable to increased detection, temporally parallels an increasing tendency to prescribe antidepressants in pregnancy. Based on indirect evidence, whether ASD in the child is associated with maternal depression during pregnancy, treatment with antidepressants, or a combination of the two remains unclear. Although we found that ASD was associated with maternal exposure to antidepressants, particularly SSRIs, compared with maternal nonexposure (depression status unknown), we did not find clear evidence on the risk when untreated depressed women were the comparison group. Any suggestion of increased risk for ASD is very concerning. In studies comparing antidepressant use with maternal nonexposure, although researchers controlled for depression, the relationship between depression, antidepressant use, and risk of ASD remained unclear. The small but statistically significant risk of ASD diagnosis with antidepressant use or depression or both is important to understand better, because treatment could mitigate this risk if severe depression underlies the association with ASD. One study examined the risk of having a diagnosis of ASD in the child, finding statistically significantly increased odds in women who were depressed during pregnancy (with and without known treatment) and a nonsignificant increase in mothers without depression during pregnancy. An interaction between depression and antidepressant treatment is possible, but it has not been fully elucidated. Nevertheless, women should be informed about the risk of ASD in their offspring if antidepressants are found more conclusively to increase this risk. Because the fraction of cases of ASD that could potentially be attributed to antidepressants in these studies is exceedingly small (0.6% to 2.5% of the study populations), prenatal antidepressant use is not a major risk factor for ASD and does not explain the increasing prevalence of autism.

Evidence on the benefits or harms of treatment of depression in the postpartum period is insufficient to draw conclusions. Women and clinicians are currently left with only evidence on nonpregnant populations and evidence on intermediate outcomes (e.g., which drugs are passed into breast milk) to guide treatment choices.

Limitations of the Review Process

Methodological limitations of the review within the defined scope included the exclusion of studies published in languages other than English and lack of a specific search for unpublished studies. The review process and results could have benefited from further refinement of the scope to limit inclusion of studies to pregnant or postpartum women with depression in both the intervention and control groups.

Gaps in the Research

A major caveat to interpreting the findings of the majority of studies of exposure during pregnancy is the role of depression itself. Most of the studies specified that women were taking an antidepressant for any reason; few reported the proportions of women with depression and even fewer used this information in their analyses. Studies of women who were taking an antidepressant during or after pregnancy but were not known to be depressed are problematic; a major drawback is that we do not know the differential baseline risk of various outcomes for the various indications for which antidepressants can be used. We know, however, that some baseline risks are associated with depression during pregnancy; this fact underscores the importance of limiting the treated group to women with depression.[4,5]

Some clinicians or investigators may still hesitate to conduct RCTs in pregnant women.[53] Nevertheless, the assumption that the comparative effectiveness of interventions in nonpregnant populations is directly applicable to pregnant women may not be valid for various reasons (e.g., differences in pharmacokinetics of the drugs); moreover, trials in nonpregnant populations do not measure outcomes specific to pregnant or postpartum women. Various groups advocate for RCTs in pregnant women;[54,55] furthermore, the U.S. Department of Health and Human Services outlines detailed rules on protecting pregnant women research subjects and their fetuses.[56] Because clinicians already prescribe antidepressants on a regular basis to pregnant women, RCTs comparing treatments and adequately measuring appropriate outcomes, with measurement of depression severity at baseline and during followup among such populations, do not necessarily increase risk to either the women or their fetuses. Comparisons of specific treatments in pregnancy are badly needed to better uncover variation in risk across drugs, even within a class. Ascertainment of exposure, including both timing and dose, must be done in a way that ensures accuracy and reliability. Outcomes should be determined by blinded evaluators, which is possible for nearly all outcomes considered here. Randomization would be the best approach to minimize potential confounding, but observational studies could also be done in a way that addresses the gaps in the research. For example, studies could identify women being treated for depression as the study population and make comparisons across treatments (including no treatment). These studies should adjust for important prognostic factors such as pre-existing illness,

depression history, depression severity, age, race, parity, socioeconomic status, and other exposures (e.g., alcohol, smoking, and other potential teratogens).

Nonpharmacological treatments are generally thought to have fewer risks than antidepressants. Nonetheless, evidence is almost entirely lacking on this point or on the question of the effectiveness of combinations of drug and nondrug treatments. Newer approaches to nonpharmacological interventions using technology such as Internet-based therapies, Web-camera counseling, and mobile phone applications are emerging. These may offer pregnant and postpartum women alternatives to more established treatments, particularly in lower income or rural populations.[57-59]

Studies of women in the postpartum period are both small and methodologically weak. These limitations leave a large gap in knowledge about treatments for a group of patients in whom RCTs could be undertaken. In addition to comparative efficacy (e.g., effects on symptoms), little is known about the benefits of treatments on important outcomes such as improving the mother-infant dyad, enhancing breastfeeding outcomes, or reducing domestic violence. The need for specifically designed research that addresses these problems is substantial.

The current evidence base is insufficient to inform clinical decisionmaking fully, because it requires knowing both benefits and harms and being able to determine the tradeoffs that individual patients might make. For example, if a medication has a lower adverse event profile but is also less effective for a given condition, prescribing it for a patient who needs therapy for that particular condition just because of a lower adverse event profile is not a reasonable therapeutic strategy. We know that depression during pregnancy and the postpartum period can lead to serious adverse outcomes for both mother and child, such that treatment is important. Research in this area needs to measure both benefits and harms simultaneously, so that results can better inform the tradeoffs that women and clinicians need to weigh.

References

1. Norwitz ER, Lye SJ. Chapter 5: Biology of parturition. In: Creasy RK, Resnick R, Iams JD, eds. Creasy and Resnik's Maternal-Fetal Medicine: Principles and Practice. 6th ed., Philadelphia: Saunders/Elsevier; 2009:69-86.
2. Dietz PM, Williams SB, Callaghan WM, et al. Clinically identified maternal depression before, during, and after pregnancies ending in live births. Am J Psychiatry. 2007 Oct;164(10):1515-20. PMID: 17898342.
3. Halbreich U, Karkun S. Cross-cultural and social diversity of prevalence of postpartum depression and depressive symptoms. J Affect Disord. 2006 Apr;91(2-3):97-111. PMID: 16466664.
4. Hallberg P, Sjoblom V. The use of selective serotonin reuptake inhibitors during pregnancy and breast-feeding: a review and clinical aspects. J Clin Psychopharmacol. 2005 Feb;25(1):59-73. PMID: 15643101.
5. Nonacs R, Cohen LS. Assessment and treatment of depression during pregnancy: an update. Psychiatr Clin North Am. 2003 Sep;26(3):547-62. PMID: 14563097.
6. Alder J, Fink N, Bitzer J, et al. Depression and anxiety during pregnancy: a risk factor for obstetric, fetal and neonatal outcome? A critical review of the literature. J Matern Fetal Neonatal Med. 2007 Mar;20(3):189-209. PMID: 17437220.
7. Henry AL, Beach AJ, Stowe ZN, et al. The fetus and maternal depression: implications for antenatal treatment guidelines. Clin Obstet Gynecol. 2004 Sep;47(3):535-46. PMID: 15326416.
8. Grote NK, Bridge JA, Gavin AR, et al. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. Arch Gen Psychiatry. 2010 Oct;67(10):1012-24. PMID: 20921117.
9. Murray L, Cooper PJ. Postpartum depression and child development. Psychol Med. 1997 Mar;27(2):253-60. PMID: 9089818.
10. Ludermir AB, Lewis G, Valongueiro SA, et al. Violence against women by their intimate partner during pregnancy and postnatal depression: a prospective cohort study. Lancet. 2010 Sep 11;376(9744):903-10. PMID: 20822809.
11. Myers E, Aubuchon-Endsley N, Bastian L, et al. Efficacy and Safety of Screening for Postpartum Depression. Comparative Effectiveness Review 106. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-2007-10066-I.) AHRQ Publication No. 13-EHC064-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2013. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
12. Hayes RM, Wu P, Shelton RC, et al. Maternal antidepressant use and adverse outcomes: a cohort study of 228,876 pregnancies. Am J Obstet Gynecol. 2012 Jul;207(1):49 e1-9. PMID: 22727349.
13. Gartlehner G, Hansen RA, Morgan LC, et al. Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. Ann Intern Med. 2011 Dec 6;155(11):772-85. PMID: 22147715.

14. Gartlehner G, Hansen, RA, Morgan, LC, et al. Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression: An Update of the 2007 Comparative Effectiveness Review. (Prepared by the RTI International–University of North Carolina Evidence-based Practice Center under Contract No. 290-2007-10056-I.) AHRQ Publication No. 12-EHC012-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2011. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

15. Freeman MP, Fava M, Lake J, et al. Complementary and alternative medicine in major depressive disorder: the American Psychiatric Association Task Force report. J Clin Psychiatry. 2010 Jun;71(6):669-81. PMID: 20573326.

16. Kayser S, Bewernick BH, Grubert C, et al. Antidepressant effects, of magnetic seizure therapy and electroconvulsive therapy, in treatment-resistant depression. J Psychiatr Res. 2011 May;45(5):569-76. PMID: 20951997.

17. Cuijpers P, Geraedts AS, van Oppen P, et al. Interpersonal psychotherapy for depression: a meta-analysis. Am J Psychiatry. 2011 Jun;168(6):581-92. PMID: 21362740.

18. Ishak WW, Ha K, Kapitanski N, et al. The impact of psychotherapy, pharmacotherapy, and their combination on quality of life in depression. Harv Rev Psychiatry. 2011 Dec;19(6):277-89. PMID: 22098324.

19. Nieuwsma JA, Trivedi RB, McDuffie J, et al. Brief psychotherapy for depression: a systematic review and meta-analysis. Int J Psychiatry Med. 2012;43(2):129-51. PMID: 22849036.

20. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(12)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality; April 2012. Chapters available at: www.effectivehealthcare.ahrq.gov.

21. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7). PMID: 1000097.

22. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR. 4th ed., text revision ed. Washington: American Psychiatric Association; 2000.

23. McDonagh MS, Jonas DE, Gartlehner G, et al. Methods for the Drug Effectiveness Review Project. BMC Med Res Methodol. 2012;12:140. PMID: 22970848.

24. Guyatt GH, Norris SL, Schulman S, et al. Methodology for the development of antithrombotic therapy and prevention of thrombosis guidelines. Chest. 2012 Feb 1;141(2 Suppl): 53S-70S. PMID: 22315256.

25. Sutton AJ, Abrams KR, Jones DR, et al. Methods for Meta-Analysis in Medical Research. Chichester, UK: John Wiley & Sons, Inc.; 2000.

26. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414): 557-60. PMID: 12958120.

27. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58. PMID: 12111919.

28. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: Grading the strength of a body of evidence when comparing medical interventions--Agency for Healthcare Research and Quality and the Effective Health Care Program. J Clin Epidemiol. 2010 May;63(5):513-23. PMID: 19595577.

29. Wisner KL, Bogen DL, Sit D, et al. Does fetal exposure to SSRIs or maternal depression impact infant growth? Am J Psychiatry. 2013 May 1;170(5):485-93. PMID: 23511234.

30. Yonkers KA, Norwitz ER, Smith MV, et al. Depression and serotonin reuptake inhibitor treatment as risk factors for preterm birth. Epidemiology. 2012;23(5):677-85. PMID: 22627901.

31. Croen LA, Grether JK, Yoshida CK, et al. Antidepressant use during pregnancy and childhood autism spectrum disorders. Arch Gen Psychiatry. 2011 Nov;68(11):1104-12. PMID: 21727247.

32. Rai D, Lee BK, Dalman C, et al. Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders: population based case-control study. BMJ. 2013 Apr 19;346:f2059. PMID: 23604083.

33. Bromley RL, Wieck A, Makarova D, et al. Fetal effects of selective serotonin reuptake inhibitor treatment during pregnancy: immediate and longer term child outcomes. Fetal Matern Med Rev. 2012;23(3-4):230-75.

34. Ross EL, Grigoriadis S, Mamisashvili L. Selected pregnancy and delivery outcomes after exposure to antidepressant medication: a systematic review and meta-analysis. JAMA Psychiatry. 2013:1-8. PMID: 23446732.

35. 't Jong GW, Einarson T, Koren G, et al. Antidepressant use in pregnancy and persistent pulmonary hypertension of the newborn (PPHN): a systematic review. Reprod Toxicol. 2012;34(3):293-7. PMID: 22564982.

36. Sockol LE, Epperson CN, Barber JP. A meta-analysis of treatments for perinatal depression. Clin Psychol Rev. 2011 Jul;31(5):839-49. PMID: 21545782.

37. Gentile S. Neonatal withdrawal reactions following late in utero exposure to antidepressant medications. Curr Womens Health Rev. 2011;7(1):18-27.

38. Wurst KE, Poole C, Ephross SA, et al. First trimester paroxetine use and the prevalence of congenital, specifically cardiac, defects: a meta-analysis of epidemiological studies. Birth Defects Res Part A Clin Mol Teratol. 2010 Mar;88(3):159-70. PMID: 19739149.

39. Ng RC, Hirata CK, Yeung W, et al. Pharmacologic treatment for postpartum depression: a systematic review. Pharmacotherapy. 2010 Sep;30(9):928-41. PMID: 20795848.

40. Kendall-Tackett K, Hale TW. The use of antidepressants in pregnant and breastfeeding women: a review of recent studies. J Hum Lact. 2010 May;26(2):187-95. PMID: 19652194.

41. Santone G, Ricchi G, Rocchetti D, et al. Is the exposure to antidepressant drugs in early pregnancy a risk factor for spontaneous abortion? A review of available evidences. Epidemiol Psichiatr Soc. 2009;18(3):240-7. PMID: 20034202.

42. Myles N, Newall H, Ward H, et al. Systematic meta-analysis of individual selective serotonin reuptake inhibitor medications and congenital malformations. Aust N Z J Psychiatry; 2013 Nov:47(11):1002-12. Epub 2013 Jun 12. PMID 23761574.

43. Grigoriadis S, VonderPorten EH, Mamisashvili L. Antidepressant exposure during pregnancy and congenital malformations: is there an association? A systematic review and meta-analysis of the best evidence. J Clin Psychiatry. 2013 Apr;74(4):e293-e308. PMID: 23656855.

44. Grigoriadis S, VonderPorten EH, Mamisashvili L. The effect of prenatal antidepressant exposure on neonatal adaptation: a systematic review and meta-analysis. J Clin Psychiatry. 2013 Apr;74(4):e309-e20. PMID: 23656856.

45. Painuly N, Heun R, Painuly R, et al. Risk of cardiovascular malformations after exposure to paroxetine in pregnancy: meta-analysis. Psychiatrist. 2013 Jun 1;37(6):198-203.

46. Gartlehner G, Hansen RA, Nissman D, et al. A simple and valid tool distinguished efficacy from effectiveness studies. J Clin Epidemiol. 2006 Oct;59(10):1040-8. PMID: 16980143.

47. Lu M, Lange L, Slusser W, et al. Provider encouragement of breast-feeding: evidence from a national survey. Obstet Gynecol. 2001;97(2):290-5. PMID: 11165597.

48. Philipp BL, Malone KL, Cimo S, et al. Sustained breastfeeding rates at a US baby-friendly hospital. Pediatrics. 2003 Sep;112(3 Pt 1):e234-6. PMID: 12949318.

49. Su LL, Chong YS, Chan YH, et al. Antenatal education and postnatal support strategies for improving rates of exclusive breast feeding: randomised controlled trial. BMJ. 2007 Sep 22;335(7620):596. PMID: 17670909.

50. Hale TW. Medications and Mother's Milk 2012: A Manual of Lactational Pharmacology. 15th ed. Amarillo, TX: Hale Publishing LP; 2012.

51. Lanza di Scalea T, Wisner KL. Antidepressant medication use during breastfeeding. Clin Obstet Gynecol. 2009 Sep;52(3):483-97. PMID: 19661763.

52. Lawrence RA, Lawrence RM. Breastfeeding: A Guide for the Medical Profession. 7th ed. St. Louis, MO: Saunders; 2011.

53. Howland RH. Update on St. John's wort. J Psychosoc Nurs Ment Health Serv. 2010 Nov;48(11):20-4. PMID: 21053786.

54. The Second Wave Initiative. Toward the Responsible Inclusion of Pregnant Women in Research. www.secondwaveinitiative.org/. Accessed February 2, 2014.

55. Moyer M. Why Pregnant Women Deserve Drug Trials. Body Politic [Blog]. January 6, 2011. http://blogs.plos.org/bodypolitic/2011/01/06/why-pregnant-women-deserve-drug-trials/. Accessed February 2, 2014.

56. Research involving pregnant women or fetuses [45 CFR Part 46B Section 204]. In Code of Federal Regulations. Title 45: Public Welfare. Part 46: Protection of Human Subjects. Subpart B: Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research. Washington: U.S. Department of Health & Human Services. Revised January 15, 2009. Effective July 14, 2009. www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.204. Accessed February 2, 2014.

57. Aguilera A, Munoz RF. Text messaging as an adjunct to CBT in low-income populations: a usability and feasibility pilot study. Profess Psychol Res Pract. 2011;42(6):472-8.

58. Boschen MJ, Casey LM. The use of mobile telephones as adjuncts to cognitive behavioral psychotherapy. Profess Psychol Res Pract. 2008;39(5):546-52.

59. Moritz S, Schilling L, Hauschildt M, et al. A randomized controlled trial of internet-based therapy in depression. Behav Res Ther. 2012;50(7-8):513-21. PMID: 22677231.

Full Report

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